1. **I noted in some of your lot line listing that the [redacted] in the APH ranged from as little as [redacted]. Some times this seems to be attributable to the patient because similar numbers are obtained from the same patient for 2 or 3 of the APH, whereas in other cases it varies a lot from the same patient. When the percentage is very low do you still follow through with the SOP and perform the [redacted] b(4) [redacted]? I assume the answer is yes, but just wanted to check. With regards to the upper end of the spectrum, when the [redacted] b(4) [redacted] is high can that be attributed to a leukapheresis problem or differences in the efficiency of apheresis equipment? Have you noted any differences in the APH quality from different apheresis sites over the years?**

Yes, every lot of sipuleucel-T is manufactured according to the same process regardless of the cellular content of the incoming apheresis.

The sipuleucel-T manufacturing process consistently [redacted] b(4) [redacted] b(4) [redacted] over a wide range of starting levels. (Refer to BLA 125197, Item 4, Section 3.2.P.2.3, Subsection 3.2, Process Capacity, page 128 of 261.) The 2 buoyant density separation steps constitute a robust method for isolating the mononuclear cells that are then cultured with PA2024 antigen to generate the activated immunotherapy product.

The causes of [redacted] in apheresis starting material obtained from prostate cancer patients are not easily identified. As noted, [redacted] levels can be patient-specific or visit-specific. Based on our experience, the variability is likely to be primarily dependent upon the current health of the clinical subject.

It is unlikely that the infrequent observation of [redacted] can be attributed to a difference in the apheresis equipment. For sipuleucel-T clinical trials, roughly 90% of all APHs were collected using the [redacted]). The remaining collections were split between the [redacted], b(4) [redacted]). Therefore, a more detailed analysis of [redacted] b(4) [redacted] levels by equipment would probably not be informative, due to the small numbers available for comparison.

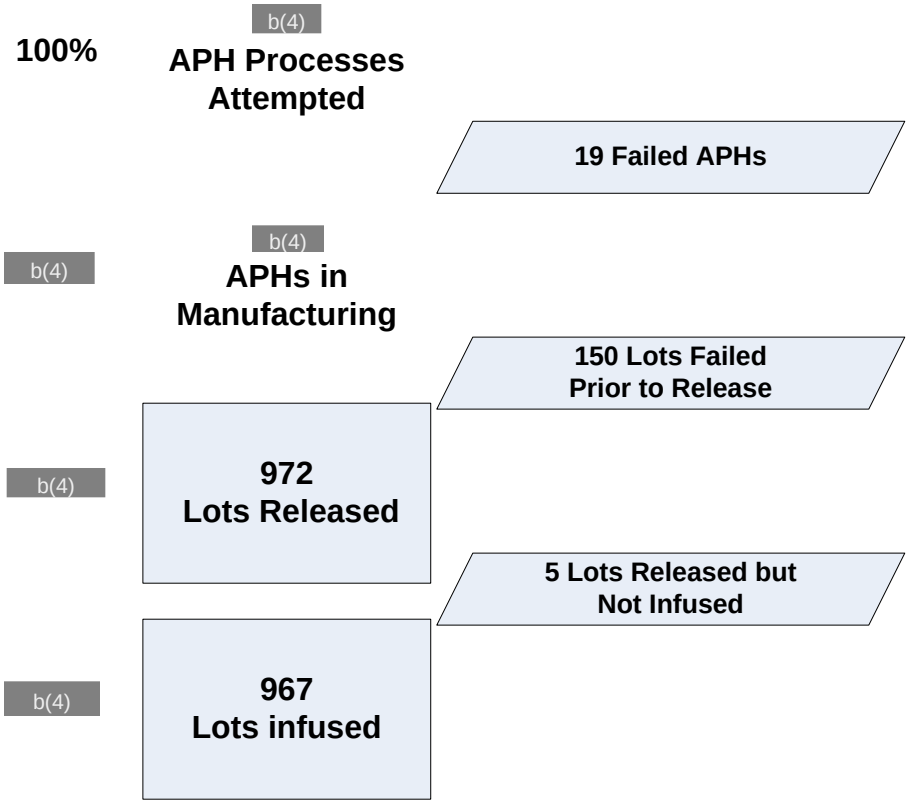
2. **In amendment 33, table 8 "Summary of leukapheresis and Product Infusions, Intent-to-Treat Population" you have indicated that for sipuleucel-T treated patients about 1/3 of subjects required a 3rd leukapheresis. Was that typically due to complications with the apheresis that required another visit, or were there situations where insufficient APH volume was collected or an in-process or final product release criterion was not met?**
3. **In amendment 33 you have listing 16.2.6.13 (begins on page 4890 of 5667) that provides a line listing on cell product parameters. It appears that roughly 10% of the time a product lot was not infused. I assume most of these were due to medical reasons. Were any of these due to a product not meeting in-process or final product release testing? Were any of them not infused because the shelf life (dating period) had expired?**

Questions 2 and 3 both relate to the causes for non-infused lots in Study D9902B: Question 2 from the apheresis stage and Question 3 from the final product stage. Answers to both questions rely on the same sets of manufacturing and clinical data. For this reason, a single response will cover both questions, referring to the same data summary tables.

Table 8 from the D9902B study report, as referenced in Question 2, contains data on how many aphereses were performed per subject, and indicates that 32.3% of the 341 Intent to Treat (ITT) subjects in the sipuleucel-T arm required more than 3 aphereses. In addressing the question of typical reasons for unsuccessful apheresis procedures, we examined all apheresis attempts that did not result in a successful infusion. This comprehensive analysis includes all subjects who required at least one repeat apheresis, regardless of the number of infusions received. Looking at the sipuleucel-T data on a per-process basis, rather than a per-subject basis, a total of b(4) apheresis procedures were attempted, resulting in 967 infusions.

Listing 16.2.6.13 from the D9902B study report, as referenced in Question 3, contains manufacturing results from b(4) APH collections that were put into production for either sipuleucel-T or placebo. (This data set excludes 19 of the b(4) leukapheresis procedures (1.7%) that failed before they entered the manufacturing queue.) The lots put into production generated 972 released lots and 967 successful infusions. Thus the overall non-infusion rate during the clinical study was b(4) (174 of b(4)). The flow chart in Figure 1 illustrates this in progressive steps.

Figure 1 Flow Chart of Sipuleucel-T Manufacturing in D9902B



The 179 unsuccessful aphereses are due to a variety of causes related to the individual subject (his health or cellular characteristics), the APH collection center, or the manufacturing process. Four categories were selected to provide an overview of the reasons for non-infusions.

- **Patient-related issues:** Includes venous access and other subject-specific collection problems, plus medical decisions not to infuse a released product.
- **Apheresis quality:** Includes collection center errors (such as improper packaging or procedural errors) and failures of APH quality attributes (such as b(4)).
- **Obsolete specifications:** Includes analytical specifications that were eliminated during the course of Study D9902B ( ) and would therefore not cause termination of a lot in the commercial setting. Also in this category are those APH expirations that occurred prior to the introduction of the b(4)-hour APH shelf life.
- **Product failures:** Includes manufacturing and equipment failures, specification failures (both in-process and final), and expirations (both APH and final product).

These categories may not be mutually exclusive, and a particular non-infused lot might be correctly attributed to more than one category. Therefore the percentages provided in Table 1

should be evaluated accordingly. For example, lots that failed in-process sterility are considered product failures, but in most cases the source of the contaminant was the patient's incoming cells, which could categorize the failure as a patient-related medical issue. However, each failed apheresis was counted only once for the table.

Table 1 Categories of Non-infused Lots of sipuleucel-T in Study D9902B

Category	Percent of All APHs Attempted n = b(4)	Percent of Non-infused Lots n = 174
Patient-related issues	1.7%	11%
Apheresis quality	2.2%	14%
Obsolete specifications	6.4%	42%
Product failures	4.6%	30%
Unknown	0.4%	3%

In summary, the overall non-infusion rate calculated from sipuleucel-T lots produced for D9902B was 15% for all reasons. The failure rate that would better reflect the current specifications and shelf life (calculated by removing the lots that failed for specifications that are now obsolete) is 8.9%.